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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,907	BOGEN ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/7/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,77 and 83-126* is/are pending in the application.

4a) Of the above claim(s) *1-37,77,84-87,93,94,97 and 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83,88-92,95,96,98-100 and 109-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-37, 77, and 83-126 are all the pending claims for this application.

2 Claims 1-37, 77, 84-87, 93, 94, 97, 101-108 are withdrawn from examination.

3. Claims 83, 91, 96, 100, 110, 113, 114, 121, 124 and 126 were amended and Claims 127-130 cancelled in the Response of 5/7/07.

4. Claims 83, 88-92, 95, 96, 98-100 and 109-126 are all the pending claims under examination with targeting units for a ligand species of soluble CD40 ligand and the chemokines, RANTES and MIP-1α, and the species of antigenic units for an antigenic scFv.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is **FINAL**.

Withdrawal of Objections

Sequence Compliance

6. The Sequence Listing of 5/7/07 for sequences disclosed in the original specification and filed pursuant to 37 CFR 1.821(c) has been considered and entered. Applicants' comments on p. 22 of the Response of 5/7/07 are acknowledged..

Specification

7. The objection to the specification for omitting to provide sequence identifiers for the following primer sequences and linker sequence pursuant to 37 CFR 1.821 (c) and/or (d): primer- p. 20, [0049]; p. 21, [0050-0051]; p. 22, [0052]; p. 22-24, [0054]; p.

24, [0056] and p. 39, [00105]; and linker- [0029], is withdrawn based on Applicants amendments to the specification as set forth on pp. 2-8 of the Response of 5/7/07. Applicants' comments on p. 23 of the Response of 5/7/07 are acknowledged.

8. The objection to [0038] for the typographical error, "C□3", is withdrawn in view of the amendment to recite "Cγ3". Applicants' comments on p. 23 of the Response of 5/7/07 are acknowledged.

9. The objection to the use of the trademarks, e.g., TRIzol® and pGEM®-T Easy Vector, is withdrawn in view of the amendment to [00105]. Applicants' comments on p. 23 of the Response of 5/7/07 are acknowledged.

Claims

10. The objection to Claims 96, 97 and 124-126 as being drawn to non-elected subject matter is withdrawn for the following reasons:

a) Claim 96 is amended to delete the non-elected species;

b) Claim 97 is withdrawn from examination; and

c) Claim 24 (and Claims 25 and 26) is amended to a vaccine composition of Claim 83 and to delete an infectious disease.

Applicants' comments on pp. 23-24 of the Response of 5/7/07 are acknowledged.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

11. The rejection of Claim 91 for the recitation "MIP-1α" is withdrawn in view of the amendment to recite "Macrophage Inflammatory Protein 1 alpha". Applicants' comments on p. 24 of the Response of 5/7/07 are acknowledged.

12. The rejection of Claims 100, 110 and 114 for the recitation "derived" is withdrawn in view of the deletion of the term from the claims. Applicants' comments on p. 24 of the Response 5/7/07 are acknowledged.

13. The rejection of Claim 13 for the recitation "substantially" is withdrawn in view of the amendment of the claim to delete the term. Applicants' comments on p. 24 of the Response 5/7/07 are acknowledged.

14. The rejection of Claims 121 and 124-126 for the recitation "degenerate variant thereof" is withdrawn in view the amendment of Claims 121 and 124 to delete the phrase. Applicants' comments on pp. 24-25 of the Response 5/7/07 are acknowledged.

Objections Maintained

Specification

15. The objection to Figures 8-11 for disclosing the linker sequences, $(GlyGlyGlySerSer)_3$ (Figures 8 and 9) and $(GlyGlyGlyGlySer)_3$ (Figures 10 and 11), with out reference to a SEQ ID NO is maintained.

Applicants did not respond to the objection in the Office Action of 11/7/06. Applicants are requested to submit new replacement drawings or to amend the respective figure legends in the specification.

Applicants are advised to carefully check the entire specification and drawings for any other sequences that require proper identification.

Rejections Maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. The rejection of Claims 118, 121, 122 and 124-126 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained for reasons of record as set forth in the Office Action of 11/7/06 and hereinafter.

Applicants have amended the originally examined claims for a nucleic acid encoding a recombinant antibody comprising two targeting units and two antigenic units to a nucleic acid encoding a monomer unit comprising a targeting unit, an antigenic unit,

a hinge and a Cγ3 domain (in unspecified structural order), and where two of a monomer unit would form a dimeric antibody.

Applicants' amendments to the claims do not overcome the rejection and instead raise new grounds for rejection as discussed infra. Applicants allegations on pp. 25-28 of the Response of 5/7/07 are addressed as follows.

Applicants allege that the nucleic acids and vectors are formulated for immunization rather than by delivery via gene therapy route. The Vaccibodies encoded by the nucleic acids are capable of inducing an immune response against multiple myeloma and the feasibility of treating animals and humans. Genetic immunization with recombinant nucleic acids by intramuscular injection or electroporation was established prior to the filing date as shown in USPN 5,580,859 and Stevenson (PNAS) and has been well known for the past 15 years. Applicants allege that unlike gene therapy which requires targeting, genetic immunization merely requires transient transfection of the nucleic acid-encoding protein into muscle cells, for example, and expression so that a "traditional immune response" is mounted against the expression products.

Examiner's Reply

The specification does not teach gene immunization (or gene therapy) methods for treating or *preventing* a cancer much less a myeloma or lymphoma or inducing a *prophylactic* T- or B-cell immune response in a *human patient* with a *nucleic acid* of the claims examined in the Office Action of 11/7/06, the vector comprising the nucleic acid or a vector-transfected cell or cell line encoding the recombinant antibody-based molecule. There are no working examples in Applicant's specification to guide the

skilled artisan in practicing the administration of the nucleic acid, vector or transfected host cell, more especially by injection and electroporation, which results in *a) induction of an immune B- and T cell response or b) a reduction in a cancer such as myeloma or lymphoma*. The goal of tumor vaccination is the induction of tumor immunity to *prevent* tumor occurrence or recurrence and Applicants have not demonstrated any such effect(s) with the nucleic acid as originally examined.

Applicants' detailed explanation of the distinction between gene immunization and gene therapy on pp. 26-27 of the Response of 5/7/07 is acknowledged. However, the pharmaceutical composition and vaccine composition claims are not in any way limited to the route of administration or that the intended use is for gene immunization rather than gene therapy.

Felgner (USPN 5,580,859) examined gene immunization using a single expression plasmid construct encoding the gp-120 protein under the CMV promoter, that when injected into mouse muscle, expressed a functional protein excreted from cells and capable of inducing an antibody response (Example 19; Figure 5). In Example 20, a cell line was transfected with the construct of Example 19, injected into mice, and an IgG and IgM response was demonstrated. Felgner does not demonstrate that the construct produced an immunogenic response, but only an antigenic response. Felgner did not demonstrate induction of a therapeutic or prophylactic immune response. Felgner demonstrates the antigenicity of a single vector construct that does not in any way resemble the instant claimed invention for a nucleic acid much less a vector encoding the nucleic acid.

A copy of the Stevenson reference was not received with the Response of 5/7/07, thus Applicants comments regarding Stevenson on pp. 27-28 are incomplete. Applicants are invited to resubmit the Stevenson reference in their Response to this Action for consideration and entry.

The Examiner submits that Claims 118, 121, 122 and 124-126 in depending from amended Claim 83 and now being drawn to a nucleic acid encoding a monomer unit for a dimeric antibody are not any more enabled for an intended use in gene immunization or gene therapy, because the instant specification does not teach how one skilled in the art could achieve with any degree of predictability the equimolar expression of each monomer unit from a different vector much less that the two monomer units could specifically dimerized in vivo to form a dimeric antibody. This aspect of the claims is discussed infra.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. The rejection of Claims 83, 88-92, 96, 98, 109-117, 119, 120 and 123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US 20050069549;

published March 31, 2005; filed Jan 14, 2003) is maintained for reasons of record as set forth in the Office Action of 11/7/06 and hereinafter.

Applicants have amended the originally examined claims for a nucleic acid encoding a recombinant antibody comprising two targeting units and two antigenic units to a nucleic acid encoding a monomer unit comprising a targeting unit, an antigenic unit, a hinge and a Cγ3 domain (in unspecified structural order), and where two each of a monomer unit would form a dimeric antibody.

Applicants allege on pp. 28-29 of the Response of 5/7/07 that the claims have been distinguished from Herman by introducing the limitation into claim 83 for a "monomer structure having two monomer units, each unit connected through a dimerization motif comprising a hinge region and a Cγ3 domain of each unit and each monomer unit lacking a CH2 domain.

The Examiner submits that Herman discloses nucleic acids for scFvs in various formats including dimers, trimers and tetraspecific formats and fusions of such antibodies to other functional moieties (e.g., toxins, cytokines, chemokines, adhesion molecules), and multispecific formats that bind at least two different specificities for different ligands on the same target cell [0107-0108].

Herman discloses multispecific ligands comprising an Fc portion and a hinge region, where the Fc portion is a partial Fc portion such as CH3 [0068]. Herman does not specifically disclaim a CH2 domain, but specifically teaches an IgG subtype CH3 domain in the absence of CH2, and where the mutispecific ligand contains an Fc portion that does not bind an Fc receptor [0052]. For those CH3 regions that bind Fc receptors,

e.g., IgE, Herman specifically discloses that the CH3 should be modified to eliminate binding [0068]. Implicit in Herman's disclosure is that the multivalent ligand should not bind Fc receptors. Herman contemplates that the heavy chain or Fc portion should also contribute to pairing or dimerization of the structure [0234] and that CH3 domains specifically are recognized as mediating cross-pairing between protein chains [0232], and the cross-pairing or dimerization would occur through inherent noncovalent interactions such as hydrophobic interactions because Herman does not explicitly or implicitly disclose engineering covalent amino acids out of the Fc or CH3 domains.

Finally, Herman discloses hinge regions used for linking two Fc domains through disulphide bonding [0116].

For all of the foregoing reasons, the rejection of the claims is maintained over Herman.

New Grounds for Objection

Claim Objections

18. Claims 109 and 112 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

a) Claim 109 is drawn to a dimerization motif comprising a hinge region and depends from amended Claim 83, which is drawn to a dimerization motif comprising a hinge region.

b) Claim 112 is drawn to a hinge region forming a covalent bond and "is a disulphide bridge", and depends from Claim 83, which is drawn to a dimerization motif comprising a hinge region that dimerizes via "disulfide bridging".

19. Claims 83 and 112 are objected to for inconsistent spelling of "disulfide" and "disulphide". Unless Applicants can identify any reason(s) why the chemical names impart any difference in claim interpretation, Applicants are requested to amend the terms for consistency.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 83, 88-92, 95, 96, 98-100 and 109-126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 83, 88-92, 95, 96, 98-100 and 109-126 recite "said monomer units" in Claim 83 and there is no antecedent basis in Claim 83. Claim 83 is drawn to a "monomer unit".

b) Claims 83, 88-92, 95, 96, 98-100, 109, and 111-126 are indefinite for the recitation "comprising a hinge region" in Claim 83, because it is not clear what kind of

hinge region or from what kind of protein the hinge should be obtained. A hinge is unlimited as to the possible number of embodiments and one cannot determine the mete and bounds of the claims.

c) Claims 88-92, 95, 96 and 98 recite "targeting units" in Claims 88, 95, 96 and 98 and there is no antecedent basis in the claims or in Claim 83 from which they depend. Claim 83 is drawn to "a targeting unit."

d) Claims 99 and 100 recite "antigenic units" in Claim 99 and there is no antecedent basis in the claim or in Claim 83 from which the claims depend. Claim 83 is drawn to "an antigenic unit."

e) Claim 109 is indefinite for the broadening recitation "wherein said dimerization motif comprises...an immunoglobulin domain", because in depending from Claim 83, the domain is required to be a Cγ3 domain.

Similarly, Claims 113-117 are rejected because they broaden the domain of Claim 83 from the required Cγ3 domain dimerizing via hydrophobic interactions.

f) Claim 111 is indefinite for the broadening recitation "where the hinge region has the ability to form one or several covalent bonds" because in depending from Claim 83, the hinge is required to form disulfide bonds by disulfide bridging.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 118, 121, 122 and 124-126 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

The interpretation of Claims 118, 121, 122 and 124-126 is of record and as discussed supra in view of amended Claim 83 for a nucleic acid monomer of a dimeric antibody.

Disclosure in the Specification

The specification does not disclose a cistronic vector encoding both monomeric units that are expressed in equimolar amounts and that would allow the expressed monomeric subunits to dimerize into a dimeric antibody in vivo. The specification teaches each monomeric unit being encoded by a vector. The specification does not disclose a) administering separate nucleic acid vectors encoding each of the monomer

units to a patient for inducing production of the dimeric antibody (Claim 118) or b) pharmaceutical compositions comprising vectors encoding a nucleic acid encoding each of a monomer unit (Claim 121) or host cells comprising vectors encoding a nucleic acid encoding each of a monomer unit (Claim 122) where the intended use is to induce a *protective* immune response against cancer such as myeloma or lymphoma in a patient or c) vaccines comprising a nucleic acid for each of a monomeric unit and the success in obtaining a fully assembled dimeric antibody that could treat or preventing cancer such as myeloma or lymphoma in a patient (Claims 124-126). The art known meaning of a vaccine is that it provide a prophylactic effect (see attached copy of Stedman's Medical Dictionary definition for "vaccine"). Thus the specification does not demonstrate with a sufficient number of working examples that the pharmaceutical compositions comprising a nucleic acid encoding a monomer unit much (of Claim 83) much less two or more nucleic acids each encoding a different monomer unit, could reasonably produce a therapeutic gene immunization effect in vivo much less in a human. Further, the specification provides no example of the vaccine compositions comprising a nucleic acid encoding a monomer unit much (of Claim 83) much less two or more nucleic acids each encoding a different monomer unit, could reasonably produce a prophylactic gene immunization effect in vivo much less in a human.

State of the Art for Gene Immunization

The Examiner incorporates the references cited by Applicants in the Response of 5/7/07 as providing the background and state of art for gene immunization protocols. Thus based on the foregoing discussion distinguishing of the Felgner reference, one

skilled in the art would not be reasonably apprised from the specification or the prior art how to use the instant claimed pharmaceutical and vaccine compositions. Further to practice using the pharmaceutical and vaccine compositions for the instant nucleic acid, one of skill in the art would be required to perform undue trial and error experimentation to determine how to express equimolar amounts of the nucleic acid encoding a monomer unit in order to be reasonably assured that two monomer units could dimerized into a dimeric antibody. For all of these reasons, the claims are not enabled as of the application filing date.

Conclusion

22. No claims are allowed.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/Larry R. Helms/

Supervisory Patent Examiner